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Chemistry of Nitrosoimines. XII.[1] Reactions of 3-Substituted 2-Nitrosoimino-2,3-dihydrobenzothiazoles with Alkyl Grignard Reagents

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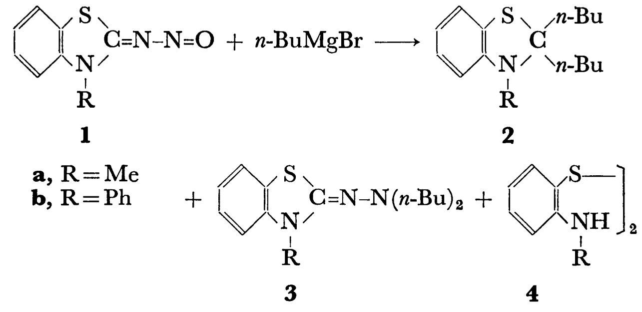
3-Substituted 2-nitrosoimino-2,3-dihydrobenzothiazole (**1**) reacts with primary or secondary alkyl Grignard reagents to afford bis[*o*-(*N*-substituted amino)phenyl] disulfide, 3-substituted 2-*N'*-alkyl- and 2-*N'*,*N'*-dialkylhydrazono-2,3-dihydrobenzothiazoles as major products. In the reactions with secondary alkyl Grignard reagents, 3-substituted 2-*N'*-alkylidenehydrazono-2,3-dihydrobenzothiazole was also produced. The general feature of the reaction of **1** with Grignard reagents has been summarized and is discussed.

In a previous paper,[2] it was reported that reactions of 3-substituted 2-nitrosoimino-2,3-dihydrobenzothiazole (**1**) with arylmagnesium or *t*-butylmagnesium halides give the corresponding 2,2-di- or 2-monosubstituted benzothiazolines in good yields (*path a*). Such Grignard reagents attack the nitrogen atom of the nitroso group of **1** to give 2-(*N'*-substituted hydrazono) derivatives (*path b*).

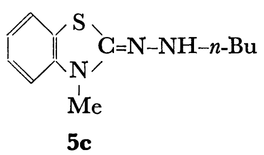
The reaction of **1** with benzylmagnesium chloride afforded 2,2-dibenzylbenzothiazolines as minor products (*path a*) and azines and 2-(*N'*,*N'*-dibenzylhydrazono) derivatives (*path b*) as major products.[1]

This paper describes the reactions of **1** with alkyl Grignard reagents in detail[3] and gives a summary of the general aspect of the reaction of **1** with Grignard reagents.

2-Nitrosoimino-3-phenyl-2,3-dihydrobenzothiazole (**1b**) reacts with excess *n*-butylmagnesium bromide in ether at 0 °C under nitrogen to afford 2,2-di-*n*-butyl- (**2b**, 6%), 2-*N'*,*N'*-di-*n*-butylhydrazono-3-phenyl-2,3-dihydrobenzothiazoles (**3b**, 26%), and bis(*o*-anilinophenyl) disulfide (**4b**, 23%).



A similar reaction of **1a** with *n*-butylmagnesium bromide was found to give 2-*N'*-*n*-butylhydrazono-3-methyl-2,3-dihydrobenzothiazole (**5c**, 20%) and bis[*o*-(*N*-methyl-*N*-valeroylamino)phenyl] disulfide (**6**, 11%) together with **2a** (7%), **3a** (15%), and **4a** (12%).



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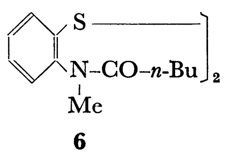

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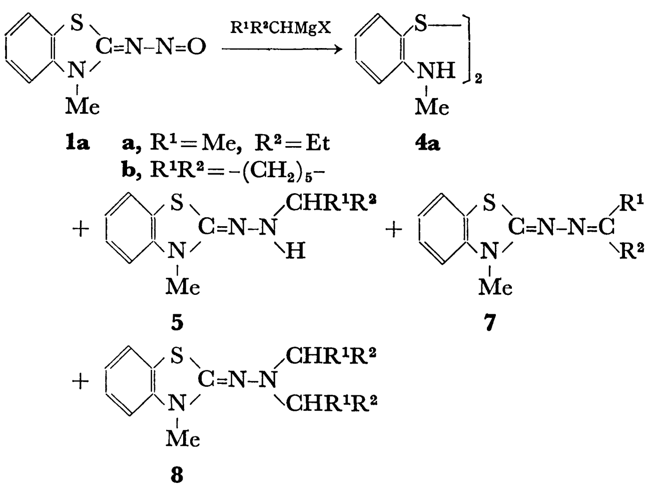
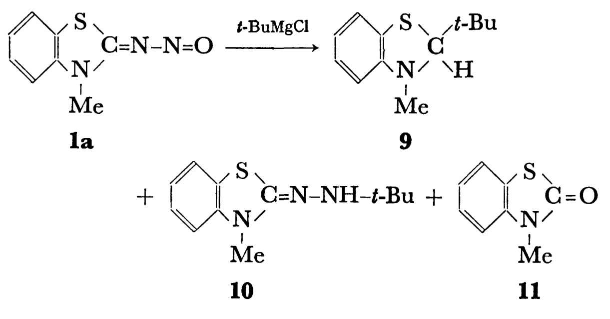
Reaction of **1a** with *sec*-butylmagnesium bromide gives **4a** (13%), 2-*N'*-*sec*-butylhydrazono- (**5a**, 18%), and 2-*N'*-*sec*-butylidenehydrazono-3-methyl-2,3-dihydrobenzothiazoles (**7a**, 22%).

Reaction of **1a** with cyclohexylmagnesium chloride gives **4a** (8%), **5b** (20%), **7b** (14%), and 2-*N'*,*N'*-dicyclohexylhydrazono-2,3-dihydrobenzothiazole (**8b**, 6%). The reaction scheme is shown below.

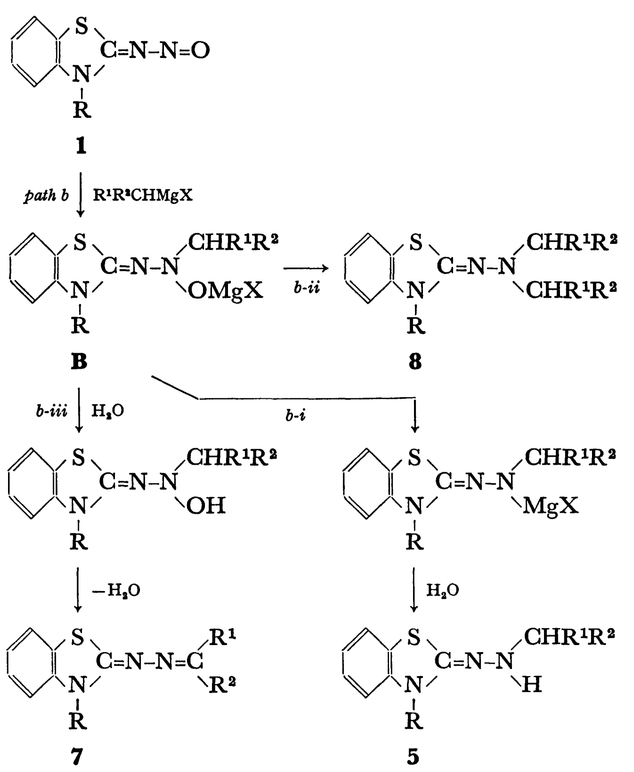


Reaction of **1a** with *t*-butylmagnesium chloride affords 2-*t*-butyl (**9**, 39%), 2-*N'*-*t*-butylhydrazono-3-methyl-2,3-dihydrobenzothiazoles (**10**, 8%), and 3-methyl-2,3-dihydrobenzothiazol-2-one (**11**, 13%).



2,2-Disubstituted and 2-(*N'*-substituted hydrazono) derivatives are formed *via* the corresponding 1,4- (**A**) and 1,2-addition intermediates (**B**), respectively.[2]

2-*N'*-Alkylidenehydrazono derivatives in the case of secondary alkylmagnesium halides are produced by dehydration through the intermediate (**B**) because of the thermodynamic stability of the product. 2-*N'*,*N'*-Dialkylhydrazono derivatives can be formed through the intermediate (**B**) by direct attack with the second Grignard reagent (*path b-ii*) as was evidenced in the reactions with benzylmagnesium chloride in refluxing ether.[1]



Scheme 1.

The formation of disulfide (**4**) can be explained as follows. The direct attack of a Grignard reagent on the C-2 position of **1** gives the diazonium intermediate (**A**) (*path a-i*) and the corresponding ring-opened nitrosoimine (**C**) followed by loss of nitrogen to give the corresponding amide (**D**) (*path a-ii*). The magnesium salt (**D**) then reacts with the Grignard reagent to afford the corresponding *S*,*N*-dimagnesium salt, which, by hydrolysis followed by oxidation, gives disulfide (**4**).

The presence of the amide (**D**) was confirmed by the isolation of **6** in the case of the reaction of **1a** with *n*-butylmagnesium bromide. Nitrogen loss from the ring-opened nitrosoimine (**C**) should proceed rapidly, as seen from the decomposition of *N*-nitrosoketimines[4] and 1,1,3,3-tetrasubstituted 2-nitrosoguanidines.[5]

The yields of reaction products of **1a** with Grignard reagents are summarized in Table 1. The yields were estimated from the amount of isolated products by column chromatography followed by recrystallization, and not optimized. The apparent yield should thus be lower than that in the reaction mixture, cases where products did not crystallize easily being affected. This was especially the case for e) in Table 1. However, it sufficiently shows the general nature of the reaction.

Table 1. Yields[a] of reaction products of **1a** with RMgX

R		Reaction path[b]			Reaction path[c]			
	X	*a-i*	*a-ii*	*a*	*b-i*	*b-ii*	*b-iii*	*b*
a) $PhCH_2$	Cl	8	—	8	—	19	44	63
b) $Me(CH_2)_3$	Br	7	23	30	20	15	—	35
c) MeEtCH	Br	—	13	13	18	—	22	40
d) *cyclo*-C_6H_{11}	Cl	—	8	8	20	6	14	40
e) Me_3C	Cl	39	—	39	8	—	—	8
f) *p*-MeC_6H_4	Br	66	—	66	17	—	—	17
g) 2,4,6-$Me_3C_6H_2$	Br	46	—	46	18	—	—	18

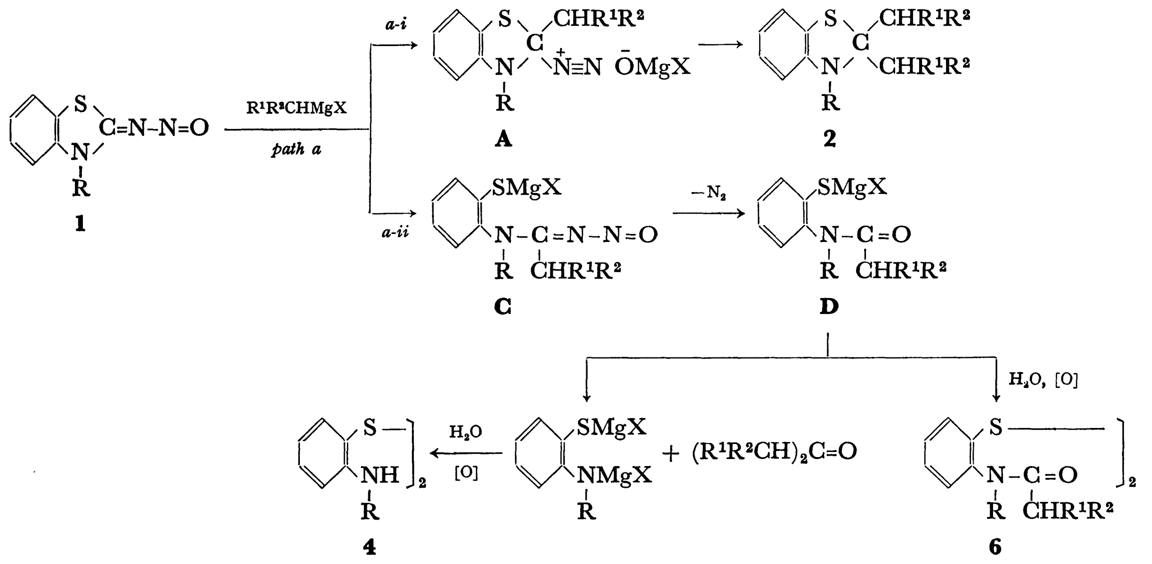
a) Numerical values show the yield (mol %) of products based on **1a**. b) *a*, *a-i*, and *a-ii* correspond to the reaction paths shown in Scheme 2. c) *b*, *b-i*, *b-ii*, and *b-iii* correspond to the reaction paths shown in Scheme 1.

It is apparent from Table 1 that Grignard reagents can be classified into two groups:

group α (more reactive), consisting of aryl and *t*-butyl groups (e—g).
group β (less reactive), consisting of primary and secondary alkyl groups (a—d).

General features of the reaction are summarized and rationalized as follows:

1) The main path of group α is *path a* and that of group β *path b* (see Schemes 1 and 2). This is consistent with the nature of the ground state of **1**[6] and the



Scheme 2.

expected relative reactivity of Grignard reagents, since ***path a*** should be of a higher energy process than ***path b***, the entire conjugation between the benzothiazoline ring and the nitrosoimino group being cut off in the former but conjugation between the ring and the imino group is retained in the latter. Here we must keep in mind that Grignard reagents add almost exclusively on the carbon of Schiff's base but not on the nitrogen.$^{7)}$

2) For ***path a***, group α reacts exclusively through ***path a-i***, whereas ***path a-ii*** is preferred by group β except benzylmagnesium chloride. This can be realized mainly by the electronic effect of the substituent (R), where R can stabilize positive charge on the C-2 more effectively, ***path a-i*** becomes predominant. It is noteworthy to mention that ***path a-i*** was not observed with secondary Grignard reagents, probably because of the balance between electronic and steric effects.

3) For ***path b***, group α reacts exclusively through ***path b-i***, whereas ***paths b-i***, ***b-ii***, and ***b-iii*** are competitive for group β. When the intermediate **B** is stabilized thermodynamically by dehydration, ***path b-iii*** is preferred as a typical one for benzylmagnesium chloride. ***Path b-ii***, alkylation of Grignard type reagent of hydroxylamine by Grignard reagent, has not been observed so far. However, this was substantiated with benzylmagnesium chloride by refluxing the solvent.$^{1)}$ The reason is not clear why group α does not follow ***path b-ii*** at all. However, it is understandable if we consider the nature of R-N-OMgX bond in the intermediate **B** (Ar-N-OMgX and *t*-Bu-N-OMgX compared with Alkyl-N-OMgX).

Experimental

Materials. 3-Methyl- (**1a**, mp 143 °C (dec.))$^{8)}$ and 3-phenyl-2-nitrosoimino-2,3-dihydrobenzothiazoles (**1b**, mp 140 °C (dec.))$^{9)}$ were prepared by the reported methods. All the reactions were carried out under nitrogen.

Reaction of 3-Methyl-2-nitrosoimino-2,3-dihydrobenzothiazole (1a) with n*-Butylmagnesium Bromide.* **1a** (4.78 g, 24.7 mmol) was added portionwise over a period of 0.5 hr at room temperature to a stirred Grignard solution prepared from magnesium turnings (2.76 g, 0.11 mol) and *n*-butyl bromide (13.82 g, 0.10 mol) in ether (100 ml). Stirring was continued for 3 hr. The reaction mixture was treated with saturated aqueous ammonium chloride and the resulting precipitates were filtered off. The precipitates were extracted with ether (100 ml×2) and benzene (100 ml). The extracts and ether layer of the filtrate were combined and dried over anhydrous magnesium sulfate. The solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel. 2,2-Di-*n*-butyl-3-methyl-2,3-dihydrobenzothiazole (**2a**, 0.49 g, 7%) was eluted with *n*-hexane as an oil. The structure of **2a** was confirmed by the following spectral data: NMR ($CDCl_3$): δ 0.53—2.13 (m, 18H, $2CH_3CH_2CH_2CH_2$), 2.67 (s, 3H, N-CH_3), and 5.95—7.16 (m, 4H, Ar-H); Mass: *m/e* 263 (M^+, 7%) and 206 (M^+-n-Bu, 100%).

Bis(*o*-methylaminophenyl) disulfide (**4a**, 0.39 g, 12%) was eluted with *n*-hexane–benzene (1: 1) and recrystallized from chloroform–ethanol, mp 66.5—67.0 °C (lit,$^{10)}$ 64—68 °C. Disulfide **4a** (0.13 g) was refluxed in acetic anhydride (8 ml) for 1 hr to give diacetylated compound (0.15 g, 87%), mp 173.0—173.8 °C (from chloroform–ethanol). IR (KBr): 1670 cm^{-1} (CO); NMR ($CDCl_3$): δ 1.85 (s, 6H, $2CH_3CO$), 3.26 (s, 6H, 2N-CH_3), and 7.05—7.72 (m, 8H, 2Ar-H); Mass: *m/e* 360 (M^+, 1.8%), 180 ($M^+/2$, 28%), and 148 ($M^+/2-S$, 100%).

Found: C, 59.76; H, 5.69; N, 7.60; S, 17.77%. Calcd for $C_{16}H_{20}N_2O_2S_2$: C, 59.97; H, 5.59; N, 7.77; S, 17.79%.

2-*N′*,*N′*-Di-*n*-butylhydrazono-3-methyl-2,3-dihydrobenzothiazole (**3a**, 1.44 g, 20%) was eluted as an oil and the structure was confirmed by the following results: IR (KBr): 1620 and 1580 cm^{-1}; NMR ($CDCl_3$): δ 0.66—1.92 (m, 14H, $2CH_3CH_2CH_2$), 2.15—2.80 (m, 4H, 2N–CH_2–*n*-Pr), 3.48 (s, 3H, N–CH_3), and 6.75—7.47 (m, 4H, Ar–H). 2-*N′*-*n*-Butylhydrazono-3-methyl-2,3-dihydrobenzothiazole (**5c**, 0.88 g, 15%) was eluted with dichloromethane, mp 66.0—66.5 °C (from chloroform–methanol). IR (KBr): 3200 (NH), 1620, and 1580 cm^{-1}; NMR ($CDCl_3$): δ 0.71—1.75 (m, 7H, $CH_3CH_2CH_2$), 3.03 (t, $J=7.0$ Hz, 2H, *n*-PrCH_2–N), 3.41 (s, 3H, N–CH_3), 4.02 (broad s, 1H, N–H, disappeared by addition of D_2O), and 6.73—7.45 (m, 4H, Ar–H); Mass: *m/e* 235 (M^+, 100%).

Found: C, 61.43; H, 7.44; N, 18.04%. Calcd for $C_{12}H_{17}N_3S$: C, 61.24; H, 7.28; N, 17.85%.

Bis[*o*-(*N*-methyl-*N*-valeroylamino)phenyl] disulfide (**6**, 0.65 g, 11%) was eluted with dichloromethane, mp 87.5—88.5 °C. The structure was confirmed by the following spectral data; IR (KBr): 1665 cm^{-1} (CO); NMR ($CDCl_3$); δ 0.58—2.20 (m, 18H, $2CH_3CH_2CH_2CH_2$), 3.23 (s, 6H, 2N–CH_3), and 7.0—7.7 (m, 8H, Ar-H); Mass: *m/e* 444 (M^+, trace) and 139 ($M^+/2+$H-*n*-PrCHCO, 100%).

Reaction of 2-Nitrosoimino-3-phenyl-2,3-dihydrobenzothiazole (1b) with n*-Butylmagnesium Bromide.* To a stirred Grignard solution prepared from magnesium (3.60 g, 0.15 mol) and *n*-butyl bromide (20.55 g, 0.15 mol) in ether (100 ml) was added **1b** (7.61 g, 29.8 mmol) portionwise at 0 °C, and the mixture was stirred for 1 hr. After the usual work-up, the reaction mixture was chromatographed on silica gel. Elution with benzene gave crude 2,2-di-*n*-butyl-3-phenyl-2,3-dihydrobenzothiazole (**2b**), which was purified by preparative thin layer chromatography with benzene–*n*-hexane (1: 3) to give pure **2b** (0.60 g, 6%) as colorless oil; NMR ($CDCl_3$): δ 0.90 (t, 6H, 2Me), 1.30—1.85 (m, 12H, $2(CH_2)_3$), and 6.75—7.40 (m, 9H, Ar–H). Elution with benzene gave tarry material (1.39 g, 23%). The IR spectrum was in agreement with that of bis(*o*-anilinophenyl) disulfide (**4b**).$^{11)}$ Elution with dichloromethane–chloroform (2: 1—1: 5) and chloroform afforded red brown tarry material (3.34 g). The compound was purified twice by preparative thin layer chromatography with dichloromethane to give colorless viscous material (**3b**), which partly solidified on being left to stand for 2 weeks. **3b** (2.75 g, 26%); mp 40.0—41.5 °C; IR (KBr): 1610 (C=N) and 1580 cm^{-1}; NMR ($CDCl_3$): δ 0.85 (t, 6H, 2Me), 1.35 (m, 8H, $2(CH_2)_2$), 2.55 (t, 4H, $2CH_2$–N), and 6.7—7.4 (m, 9H, Ar–H); Mass: *m/e* 353 (M^+, 40%) and 310 ($M^+-C_3H_7$, 100%).

Reaction of 1a with sec*-Butylmagnesium Bromide.* **1a** (4.60 g, 23.8 mmol) was added portionwise over a period of 0.5 hr at room temperature to a stirred solution of Grignard reagent prepared from magnesium (2.77 g, 0.11 mol) and *sec*-butyl bromide (13.78 g, 0.10 mol) in ether (100 ml). Stirring was continued for 2 hr. The resulting reaction mixture was chromatographed on silica gel after the usual work-up. Bis(*o*-methylaminophenyl) disulfide (**4a**, 0.42 g, 13%) was eluted with *n*-hexane–benzene (1: 1) and the structure was confirmed by comparing its physical properties with those of an authentic sample.$^{2)}$ 2-*N′*-*sec*-Butylidenehydrazono-3-methyl-2,3-dihydrobenzothiazole (**7a**, 1.47 g, 22%) was eluted with benzene, benzene–dichloromethane (3: 1 and 1: 1) and dichloromethane, mp 81.5—82.5 °C (from chloroform–ethanol). IR (KBr): 1635 and 1580 cm^{-1}; NMR ($CDCl_3$): δ 1.15 (t, $J=7$ Hz, 3H, $=\overset{|}{C}-CH_2C\underline{H}_3$), 2.04 (s, 3H, $=\overset{|}{C}-CH_3$), 2.34 (q, $J=7$ Hz, 2H, $=\overset{|}{C}-C\underline{H}_2CH_3$), 3.44 (s, 3H, N–$CH_3$), and 6.65—7.39 (m, 4H, Ar–H); Mass: *m/e* 233 (M^+, 100%).

Found: C, 62.01; H, 6.53; N, 17.77; S, 13.72%. Calcd for $C_{12}H_{15}N_3S$: C, 61.77; H, 6.48; N, 18.01; S, 13.74%.

2-*N'*-*sec*-Butylhydrazono-3-methyl-2,3-dihydrobenzothiazole (**5a**, 1.05 g, 18%) was eluted with dichloromethane as an oil. The structure was confirmed by the following spectral data: IR (neat): 3200 cm^{-1} (NH); NMR ($CDCl_3$): δ 1.05 (t, J=7 Hz, 3H, $C\underline{H}_3$-CH_2), 1.10 (d, J=7 Hz, 3H, $C\underline{H}_3$-CHEt), 3.45 (s, 3H, N-CH_3), 3.82 (broad s, 1H, N-H), and 6.78—7.60 (m, 4H, Ar-H). Two multiplets, assignable to a methine proton and two methylene protons, overlapped each other.

Reaction of **1a** *with Cyclohexylmagnesium Chloride.* **1a** (4.47 g, 23.1 mmol) was added portionwise over a period of 0.5 hr at room temperature to a stirred solution of Grignard reagent prepared from magnesium (2.75 g, 0.11 mol) and cyclohexyl chloride (11.78 g, 99 mmol) in ether (100 ml). Stirring was continued for 4 hr. The reaction mixture was chromatographed after the usual work-up. 2-*N'*,*N'*-Dicyclohexylhydrazono-3-methyl-2,3-dihydrobenzothiazole (**8b**, 0.49 g, 6%) was eluted with *n*-hexane-benzene (1: 1), mp 121—122 °C (from ethanol). IR (KBr): 1615 and 1590 cm^{-1}; NMR ($CDCl_3$): δ 0.87—2.15 (m, 20H, 10CH_2), 2.85 (broad s, 2H, 2CH), 3.47 (s, 3H, N-CH_3), and 6.67—7.36 (m, 4H, Ar-H); Mass: *m*/*e* 343 (M^+, 42%) and 150 ($M^+-C_6H_{11}$-$C_6H_{10}N_2$, 100%).

Found: C, 70.11; H, 8.73; N, 12.24; S, 9.42%. Calcd for $C_{20}H_{29}N_3S$: C, 69.93; H, 8.51; N, 12.23; S, 9.33%.

Bis(*o*-methylaminophenyl) disulfide (**4a**, 0.27 g, 8%) was eluted with *n*-hexane-benzene (1: 1), mp 66.5—67.0 °C (from chloroform-ethanol) (lit,[10] 64—68 °C). 2-*N'*-Cyclohexylidenehydrazono-3-methyl-2,3-dihydrobenzothiazole (**7b**, 0.89 g, 14%) was eluted with benzene-dichloromethane (1: 3) as yellow crystals, mp 114.5 °C (from benzene-chloroform). IR (KBr): 1620, 1580, and 1575 cm^{-1}; NMR ($CDCl_3$): δ 1.4—2.9 (m, 10H, 5CH_2), 3.50 (s, 3H, N-CH_3), and 6.74—7.46 (m, 4H, Ar-H); Mass: *m*/*e* 259 (M^+, 59%) and 121 ($C_7H_9N^+$, 100 %).

Found: C, 65.02; H, 6.86; N, 16.32; S, 12.50%. Calcd for $C_{14}H_{17}N_3S$: C, 64.83; H, 6.61; N, 16.20; S, 12.36%.

2-*N'*-Cyclohexylhydrazono-3-methyl-2,3-dihydrobenzothiazole (**5b**, 1.21 g, 20%) was eluted with benzene-dichloromethane (1: 1) as pale yellow crystals, mp 112.5—114.0 °C (from chloroform-ethanol). IR (KBr): 3175 (NH), 1618, 1600, and 1580 cm^{-1}; NMR ($CDCl_3$): δ 0.85—2.18 (m, 10H, 5CH_2), 2.95 (broad s, 1H, $>$CH), 3.41 (s, 3H, N-CH_3), 3.50 (broad s, 1H, N-H), and 6.65—7.44 (m, 4H, Ar-H). The singlet at δ 3.50 disappeared by addition of D_2O, a new singlet due to HDO appearing at δ 4.61. Mass: *m*/*e* 261 (M^+, 100%).

Found: C, 64.29; H, 7.23; N, 16.29; S, 12.37%. Calcd for $C_{14}H_{19}N_3S$: C, 64.33; H, 7.33; N, 16.08; S, 12.27%.

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